PROPOSAL BY COUNCIL ON RADIONUCLIDES AND RADIOPHARMACEUTICALS

FOR A REGULATION GOVERNING EVALUATION AND APPROVAL OF

DIAGNOSTIC RADIOPHARMACEUTICALS

January 14, 1998

PART 315 - RADIOPHARMACEUTICALS FOR DIAGNOSIS OR MONITORING

Subpart A -- General Provisions

§ 315.1- Scope of this part.

(a) This part implements section 122 of the Food And Drug Administration Modernization Act of 1997, and sets forth special criteria and considerations to be taken into account in FDA's review, under section 505 of the act or section 351 of the Public Health Service Act, of the safety and effectiveness Of radiopharmaceuticals intended for diagnosis or monitoring of diseases or manifestations of diseases in humans. A radiopharmaceutical covered under this section is also subject to part 314 of this subchapter if it is a new drug, or Part 314 of this subchapter and § 601.2(b) of this chapter if it is a biological.

(b) Radiopharmaceuticals that are intended for therapeutic uses rather than diagnostic or monitoring uses are not subject to this part.

§ 315.2. Definition.

For purposes of this part, *diagnostic radiopharmaceutical* means -

(a) an article -

(1) that is intended for use in the diagnosis or monitoring of a disease or manifestation of a disease in humans; and

(2) that exhibits spontaneous disintegration of unstable nuclei with-the emission of nuclear particles or photons; or

(b) any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of such article.

Subpart B -- Determination of the Safety and Effectiveness of Diagnostic Radiopharmaceuticals

§ 315.10 Factors to be taken into account in general.

FDA's determination of the safety and effectiveness of a diagnostic radiopharmaceutical shall include consideration of the following:

(a) the proposed use of the diagnostic radiopharmaceutical in the practice of medicine;

(b) the pharmacological and toxicological activity of the diagnostic radiopharmaceutical (including any carrier or ligand component of the diagnostic radiopharmaceutical); and

(c) the estimated absorbed radiation dose of the radiopharmaceutical.

§ 315-11 indications for diagnostic radiopharmaceuticals.

(a) Diagnostic radiopharmaceuticals are often non-specific with regard to a particular disease, and a single diagnostic radiopharmaceutical may provide morphological or physiological information in patients suffering from a variety of diseases. This information, along with other clinical data, is used by the physician to assess the patient and decide upon a final diagnosis or treatment plan. Diagnostic radiopharmaceuticals are generally not used alone to diagnose a specific disease. Where a diagnostic radiopharmaceutical is intended to provide information (for example, a functional assessment of an organ system or a biochemical characterization of a body process) that is not disease-specific, it may be appropriate for the labeled indication to refer to more than one disease, or not to refer to any specific disease.

(b) The major categories of indications for diagnostic radiopharmaceuticals include, but are not limited to, the following:

(1) Structure localization, such as the delineation of the gastrointestinal tract or enhancement of a vessel.

(2) *Functional assessment* of an organ or body system, such as ejection fraction, myocardial wall motion or cerebral perfusion. Functional assessments require a qualitative or quantitative understanding of a parameter (the quantitative parameter need not be absolute) along with the confidence interval for that parameter in normal subjects.

(3) *Biochemical* characterization, such as a marker of glucose utilization or a specific receptor. Biochemical indications focus on determining if the measured parameter is within normal limits and require a qualitative or quantitative understanding of the parameter (the quantitative parameter need not be absolute) along with the confidence interval for that parameter in normal subjects.

(4) *Disease/organ specific,* such as the use of a monoclonal antibody for the detection of a tumor subtype or the use of labeled cells for the detection of infection or thrombus.

(5) *Management decision making,* such as the assessment of post revascularization outcome in patients with coronary artery disease; the resectability of a patient with recurrent disease; tissue viability; the prognosis of the patient's disease; or interventional outcome. Diagnostic radiopharmaceuticals having these indications provide information leading directly to a patient management decision.

§ 315.12 Evaluation of effectiveness.

(a) A diagnostic radiopharmaceutical shall be considered to be effective if it provides accurate information that contributes to a patient's diagnosis, monitoring, or treatment. Depending on the indication sought, this may be demonstrated by the diagnostic performance of the radiopharmaceutical (for example, sensitivity and specificity, or by other measures of the accuracy of the information provided. A sponsor shall not he required to demonstrate that a diagnostic radiopharmaceutical effects a change in diagnosis or in patient management, unless the proposed labeling contains claims that the diagnostic radiopharmaceutical is effective for such uses.

(b) The acceptable measures of effectiveness of a diagnostic radiopharmaceutical depend on the proposed indication. Following are the types of measures of effectiveness that are acceptable for each of the indication categories described in 315.11(b):

(1) For diagnostic radiopharmaceuticals described in 315.11(b)(1), the primary measure is the ability to locate and characterize the structure, with minimal determination of normal or abnormal appearance.

(2) For diagnostic radiopharmaceuticals described in 315.11(b)(2) and (3), the primary measure is a qualitative or quantitative determination of a known parameter, along with the confidence interval for that parameter in normal subjects.

(3) For diagnostic radiopharmaceuticals described in 315.11(b)(4), the primary measures are the sensitivity and specificity of the drug to identify or detect the disease.

(4) For diagnostic radiopharmaceuticals described in § 315.11(b)(5), the primary measure is the impact of the imaging test on management decisions and the outcomes of those decisions.

For indications that do not fall within the categories identified § 315.11(b), the sponsor should consult with FDA on the types of measures to be used to evaluate effectiveness.

(c) *Clinical investigations of diagnostic radiopharmaceuticals for non-disease-specific indications.* In addition to the traditional approach to clinical trial design applicable to disease-specific indications, two alternative clinical trial designs shall be acceptable for the approval of a diagnostic radiopharmaceutical where the proposed indication involves a functional assessment or biochemical characterization that is not disease specific:

(1) Model approach. This type of clinical trial focuses on representative diseases that involve the processes for the indication being sought, such as altered wall motion or abnormal anatomy. The process may be extrapolated to other disease states based on the common process rather than the specific disease.

(2) Multiple *small cohort approach.* This trial design allows for *a priori* stratification of patients into specific cohorts, such as diseases, as patients are enrolled in the trials. The sponsor and FDA shall agree on the number of patients in each cohort to be evaluated.

(d) *Endpoints.*

(1) Primary endpoints may be based on the determination of lesion size, the number of lesions, other characteristics of the detected disease or the manifestation of disease, or confidence in a diagnosis. Approval of a diagnostic radiopharmaceutical shall not require a showing of equivalence or superiority to radiopharmaceuticals already approved.

(2) Measurable secondary endpoints, such as staging of disease (where the primary endpoint is detection of disease), or total test study procedure time, may be used to support diagnostic claims. The evaluation of image quality or clarity is subject to individual investigator preferences, and generally should not be used as a secondary endpoint.

(e) *Cooperators.*

(1) "Gold Standards." For a diagnostic radiopharmaceutical developed for an indication for which another diagnostic radiopharmaceutical is currently approved, a direct comparison to the approved radiopharmaceutical may generate adequate evidence of effectiveness for FDA approval. The comparison may be based on image characterization such as visualization and/or pathology of organs, determination of extent of pathology, measurement of signal intensity, or performance measures.

(2) When there is no approved radiopharmaceutical to compare with the radiopharmaceutical being investigated, accuracy shall be verified by an independent assessment of the disease using another diagnostic modality which has been previously established as safe and effective for the proposed indication, or using available clinical information (for example, observation at surgery or histopathology).

(f) Use of placebo control. Placebo controls generally are not needed for the evaluation of the effectiveness of a diagnostic radiopharmaceutical.

(g) *Blinded vs. unblinded readers.*

(1) A blinded read shall be integrated into a study protocol except when a comparative agent is used, or when the primary investigator is blinded to the identity of the study drug or dose. In these circumstances, a standard clinical diagnosis (final diagnosis) shall be sufficient.

(2) Blinded reads are conducted in an artificial setting with little clinical information available to the reader. Efficacy shall be determined by both the results of the blinded read and the clinical investigator's diagnosis, with the results of the blinded read used to support the final clinical diagnosis.

(h) *Paired vs. unpaired image evaluation.* In a clinical setting where an unenhanced image is used in the clinical evaluation, an unpaired design is required. In a clinical setting where the enhanced image is intended to augment the baseline study, a paired design is required unless an unpaired design is justified by the sponsor.

§ 315.13 Evaluation of Safety.

(a) Diagnostic radiopharmaceuticals typically are well tolerated at all dose levels, and the safety profile of a given diagnostic radiopharmaceutical is relatively predictable based on the type of agent. FDA's safety assessment shall be based on the class of the diagnostic radiopharmaceutical, as described in subsection (b).

(b) Classification. For purposes of evaluating safety, FDA classifies diagnostic radiopharmaceuticals as follows:

(1) *Class 1* - Diagnostic radiopharmaceuticals that are chemical entities administered at tracer quantity levels that do not have the potential for eliciting a pharmacological response.

(2) Class 2 - Diagnostic radiopharmaceuticals containing biological materials that are administered at tracer quantity levels, but have the potential for eliciting allergic type responses. The risk of sensitization to the agent shall be evaluated.

(3) *Class 3* - Diagnostic radiopharmaceuticals administered at mass levels at which the potential for a pharmacological response is theoretically possible. The specific activity of the drug is critical in evaluating the potential risks. Extensive safety evaluations shall be conducted in a limited number of patients in Phase I investigations.

(c) *Adverse events.* An adverse event may be due to the underlying disease, the anxiety of the patient, or the imaging procedure itself. Historical data concerning the rate and types of adverse events associated with a particular modality, independent of the agent being administered, may be useful in defining the true adverse event profile for a diagnostic radiopharmaceutical. A placebo may also be useful in safety assessment. Adverse events caused by a placebo may be used in establishing the safety profile of a diagnostic radiopharmaceutical and shall be described in the labeling.

(d) *Dosage determination.*

(1) Diagnostic radiopharmaceuticals typically have no pharmacologic effect and no toxicity throughout the entire dose range. A maximum tolerated dose is not required to be established for a Class 1 or Class 2 diagnostic radiopharmaceutical but may be required for a Class 3 diagnostic radiopharmaceutical. Ordinarily, the dose of a diagnostic radiopharmaceutical shall be based on the amount of radiation the patient will absorb, rather than pharmacologic action or adverse events associated with the agent.

(2) Dosimetry estimates shall be based on the biodistribution data collected in at least one animal species and in a limited number of human subjects. Occupational radiation dose limits (see, e.g., 21 C.F.R. part 20, subpart C) are not an appropriate benchmark for establishing the radiation dose of a diagnostic radiopharmaceutical.

(3) The appropriate dosage for a diagnostic radiopharmaceutical shall be the lowest effective dose. The determination of the appropriate dosage range is based on the class of the diagnostic radiopharmaceutical.

(i) For Class I diagnostic radiopharmaceuticals, dose-ranging studies generally are not necessary. Instead, the lower limit of the dosage range may be established based on mathematical and/or physical models (i.e., phantoms), and the upper limit based on acceptable radiation dosimetry estimates.

(ii) For Class 2 diagnostic radiopharmaceuticals, because of the potential for antigenic response, the appropriate dose is the lowest protein dose with the highest radioactive dose (i.e., high specific activity).

(iii) For Class 3 diagnostic radiopharmaceuticals, the upper limit of the dose range is the mass dosage that could potentially elicit a clinically observable pharmacological response, and the lower limit is the minimum radioactivity dosage needed for a satisfactory image.

(e) *Toxicity studies.* Preclinical studies of chronic toxicity, reproductive toxicity, and carcinogenicity (other than mutagenicity) ordinarily will not be necessary to establish the safety of a diagnostic radiopharmaceutical. Acute toxicity studies may be necessary for Class 3 diagnostic radiopharmaceuticals.